REMARKS

Claims 1-15 and 18-26 currently are pending in the present application and stand rejected. Applicants note with appreciation that the restriction requirement has been withdrawn and all claims have been examined in the first instance.

As an initial matter, the Office has indicated that the phrase "accumulated levels of p53" was interpreted to include all cells, based on the assertion that the specification did not define this phrase. Applicants respectfully traverse this claim interpretation and refer the Office to text in the specification at paragraphs 7 and 11. A person of skill, reading this specification would readily understand from paragraph 7, which states that "the p53 protein is accumulated by missense mutations in exons 5 through 9, making possible immunohistochemical staining (IHCS) of mutant cells," that not all cells have accumulated p53 as described in this specification. Cells with accumulated p53, as defined here, are due to mutations in specific locations and are identified by staining to detect these mutations. Again, in paragraph 11, the specification states that cells containing accumulated levels of p53 may be identified by immunohistochemical staining. Therefore, in its broadest

interpretation, only cells as described here, which contain p53 missense mutations in exons 5-9 are cells with "accumulated levels of p53" as used in this specification. Any person of ordinary skill would understand and interpret this claim phrase in light of this definition in the specification. Applicants therefore request that the Office reconsider the claims with this narrower interpretation of cells with accumulated levels of p53.

Claims 11, 18 and 19 have been rejected as indefinite under 35 U.S.C. §112, second paragraph, for recitation of the phrase "at least about." Applicants traverse this rejection and request reconsideration of claims 11, 18 and 19. The Office has a long history of accepting both "at least" and "about" as definite claim terms. See M.P.E.P. §§ 2173.05(b)(A) and 2173.05(c)(II).

Claims 1, 5, 8-10 and 26 are rejected as anticipated by Jonason, in view of the broad interpretation of the phrase "accumulated levels of p53." Applicants have explained above why this interpretation is not correct in light of the language defining "accumulation" in the specification above. Applicants submit that the rejection of claim 1 and its dependent claims 5, 8-10 and 26 should be reconsidered in light of the statements in the Office Action concerning claim interpretation and therefore request that this rejection be withdrawn.

Claims 1, 5, 7-10 and 26 are rejected as anticipated by Diamandis, also in view of the broad interpretation of the phrase "accumulated levels of p53." Applicants have explained above why this interpretation is not correct in light of the language defining "accumulation" in the specification above. Applicants submit that the rejection of claim 1 and its dependent claims 5, 7-10 and 26 should be reconsidered in light of the statements in the Office Action concerning claim interpretation and therefore request that this rejection be withdrawn.

Claims 1, 2, 4 and 6 are rejected as anticipated by Miyajima et al. Applicants traverse this rejection. Miyajima et al. is cited for disclosure of a method involving amplification of p53 DNA from cells to determine the presence of mutations. This reference, however, is not cited for teaching amplification of DNA from a single identified cell. As such, the Office has not made out a case of anticipation since the reference does not disclose each and every element of the claims under rejection. Applicants therefore request that this rejection be withdrawn.

Claims 12 and 20 are rejected as obvious over Jonason et al. as evidenced by Brash et al. and Klein. Applicants traverse this rejection. These references are cited for disclosure of various methods used in determination of p53 mutations. However, none of

the Jonason, Brash or Klein references teach a PCR method that provides the unexpected results achieved by the present invention. The invention disclosed and claimed here is able to amplify DNA to produce a PCR product of over 1 kb in size (see Figure 2, which shows amplification products of 2 kb), which had not been achieved by the cited authors. Applicants submit that this evidence of unexpected results obviates any rejection based on obviousness since the previous methods were not able to achieve these results from amplification of the DNA from a single, identified cell.

Interestingly, the Office does not cite any disclosure in Jonason et al. of amplification of DNA from one cell but instead refers to total genomic DNA "from the cells." The claims here require amplification of DNA from an identified somatic cell. There is no expectation for success should the methods of Jonason be combined with those of Klein, for example, would be successful at achieving amplification of single-cell DNA, much less the unexpected result of surprisingly long PCR products such as were achieve here. Applicants therefore request withdrawal of this rejection.

Claim 13 is rejected as obvious over Jonason as evidenced by Brash, Klein and Goldsworthy. Applicants traverse this rejection

for the same reasons as discussed immediately above. The references would not be combined with a reasonable expectation that the PCR methods used to amplify a product from a single, identified cell would possibly result in such a highly successful amplification product with a length of over 1 kb and in fact of 2 kb. None of the methods cited, either alone or in combination were able to achieve this result, therefore an expectation of success when combining them is not present. Applicants therefore request that the Office withdraw this rejection.

Claim 14 is rejected as obvious over Jonason as evidenced by Brash, Klein and Aghassi. This combination of references is no more likely to succeed than those used in the rejection of claim 13 above. There is no reason for the person of ordinary skill to expect that these methods could achieve successfully the 1 or 2 kb long amplification products from a single, identified cell as the inventors here have achieved. Applicants therefore also request that the Office withdraw this rejection.

Claim 15 is rejected as obvious over the combination of Jonason, Brash and Klein. As discussed above, there is no expectation that combining these methods could successfully achieve 1-2 kb long amplification products from a single,

identified cell as the inventors here have achieved. Applicants therefore also request that the Office withdraw this rejection.

Claim 25 is rejected as obvious over Jonason, Brash, Murphy and Buck. The Office here relies not only on combining disclosures of methods which would have no expectation of success when combined, but also on teaching of a "functionally equivalent" primer when the primer recited in the claim is not disclosed. It is hornbook law that the cited references must contain all elements of the claim for a rejection under the obviousness statute to be proper. For this reason alone the rejection should be withdrawn. In addition, however, the Office did not present any evidence of why the primers recited in claim 25 are "functionally equivalent," particularly in light of the superior results achieved with the present invention in producing surprisingly long PCR products from amplification of DNA from a single cell. The test sequence of Buck was only 300 bp long and cannot provide a reasonable expectation of success as the present invention achieved. Applicants therefore request that this rejection be withdrawn.

Claims 2, 3 and 6 are rejected as obvious over Diamandis and Hearslev. The Office cites Diamandis as amplifying DNA from patient cells. Diamandis obtained DNA from patient samples, but

the Office has pointed to no disclosure from this reference that the PCR was performed to amplify DNA from a single, identified cell as is claimed here. Nothing in the Hearslev reference makes up for this glaring deficiency. Applicants respectfully submit that the Office cannot make out a prima facie case of obviousness based on these references, which, even in combination, do not disclose or suggest the single cell amplification claimed here and which do not provide any hint of a reasonable expectation of success for the methods achieved here.

Claim 11 is rejected as obvious over Diamandis and Leutenegger. The deficiencies of the disclosures of Diamandis are discussed above. Leutenegger is cited for disclosure of calf thymus carrier DNA. This teaching does not make up for these deficiencies and does not provide a reasonable expectation that if the methods of Diamandis were performed on single identified somatic cells, PCR products of 1-2 kb length would be produced successfully. Applicants therefore request that the Office withdraw this rejection.

Claim 12 is rejected as obvious over Diamandis, Hearslev and Klein. The Office has combined disparate techniques from unconnected references to make this rejection. Applicants submit that even if the references were combined, which would be

unlikely given the state of knowledge by the person of skill, there would be no expectation that these cobbled-together methods would be able to achieve the long PCR amplification products from a single identified cell. None of the methods cited were able to achieve this result on their own, therefore there would be no expectation that combining them would produce the surprisingly good result provided by the claimed method. Applicants request that the rejection be withdrawn.

Claim 13 is rejected as obvious over Diamandis, Hearslev, Klein and Goldsworthy. The Office again has combined disparate techniques from unconnected references to make this rejection. Applicants traverse this rejection on the same grounds as the rejection discussed immediately above and request that the Office withdraw the rejection.

Claim 14 is rejected as obvious over Diamandis, Hearslev, Klein and Aghassi. As discussed immediately above, the Office again has combined disparate techniques from unconnected references to make this rejection, providing no reasonable expectation of success given the surprisingly superior results achieved by the present invention. Applicants traverse this rejection on the same grounds as the rejection discussed with

respect to claim 12 above and request that the Office withdraw the rejection.

Claim 15 is rejected as obvious over Diamandis and Klein. This rejection also is based on a combination of references that provide no basis for a reasonable expectation that the beneficial results achieved by this invention and discussed above could be successful. For the reasons discussed above, Applicants traverse this rejection and request its withdrawal.

Claim 18 is rejected as obvious over Diamandis and Leutenegger as applied to claim 11 and further in view of Shamsher, Felix and Buck. Applicants refer the Office to the discussion above with respect to claim 11. The combined teachings of these references do not provide a reasonable expectation that if the methods of Diamandis were performed on single identified somatic cells, PCR products of 1-2 kb length would be produced successfully. The additional three references do not teach or suggest any method which would provide a reasonable expectation that the inventive methods could be performed to obtain the results obtained as discussed above. Applicants also refer the Office to the discussion concerning "functionally equivalent" primers with respect to claim 25 in

response to this rejection. Applicants therefore request that the Office withdraw this rejection.

Claim 19 is rejected as obvious over Diamandis, Leutenegger, Shamsher, Accession No. X54156 and Buck. This rejection is based on essentially the same type of information as the rejection of claim 18 immediately above. Applicants refer the Office to this discussion and request that the rejection be withdrawn.

Claims 21-24 are rejected as obvious over Diamandis, Hearslev, Klein and Chang. The deficiencies of Diamandis, Hearslev and Klein are discussed above. Chang is cited only for teaching p53 gene therapy in cancer chemotherapy, a technology not related to the claims herein. Chang adds nothing to edify the reader concerning whether the combination of the disparate disclosures of Diamandis, Hearslev and Klein could reasonably be expected to successfully achieve the invention of these claims, which are dependent from claim 1 and contain all the limitations thereof. Applicants submit that the Office cannot meet its requirement to show a reasonable expectation of success given the surprising results achieved here with respect to PCR product length. Applicants therefore request that the Office withdraw this rejection.

Claim 25 is rejected as obvious over the combination of Diamandis, Murphy and Buck. The deficiencies of the Diamandis reference have been discussed above at length. The disclosures of Murphy and Buck also have been addressed with respect to the rejection of claim 25 above. Applicants refer the Office to these discussions concerning the lack of a reasonable expectation of success should these references be combined and request that the rejection of claim 25 be withdrawn.

Based on the arguments above with respect to claim construction and the content of the cited art, Applicants request that the Office reconsider the rejection of the pending claims.

<table>
<tr><td colspan="6">RESPECTFULLY SUBMITTED</td></tr>
<tr><td>NAME AND REG. NUMBER</td><td colspan="5">Martha Cassidy, Registration No.: 44,066</td></tr>
<tr><td>SIGNATURE</td><td colspan="2"></td><td>DATE</td><td colspan="2">October 20, 2004</td></tr>
<tr><td>ADDRESS</td><td colspan="5">Rothwell, Figg, Ernst & Manbeck
Suite 800, 1425 K Street, N.W.</td></tr>
<tr><td>CITY</td><td>Washington</td><td>STATE</td><td>D.C.</td><td>ZIP CODE</td><td>20005</td></tr>
<tr><td>COUNTRY</td><td>U.S.A.</td><td>TELEPHONE</td><td>202-783-6040</td><td>FAX</td><td>202-783-6031</td></tr>
</table>